Specialty Conference

Liver Conference

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Taken from the weekly Liver Conference at the Los Angeles County-University of Southern California Medical Center, November 30, 1970

DR. GOLDSTEIN:* A four-year-old white girl was first seen in our Pediatric Admitting Room 18 April 1970 because of fever, vomiting, light colored stools and jaundice of two to three days' duration. Laboratory tests were ordered and she was sent home with a diagnosis of probable viral hepatitis. Symptoms of acute illness subsided but jaundice remained. She was brought back to LAC-USCMC 20 April 1970 because of a severe nosebleed and was admitted to the hospital.

Past history was negative except for occasional nosebleeds over a two-year period. The family doctor had detected anemia during a routine check-up one month previously, and had prescribed an iron-B complex liquid preparation. Jaundice had not been noted previously. She had had no blood transfusions and no injections except for immunizations during her first year.

Physical examination on April 20 showed moderate jaundice and lethargy. Vital signs were: temperature 99.6° F, pulse rate 140 and respiratory rate 20 per minute. Kayser-Fleischer rings were not seen. The liver edge was firmer than normal, moderately tender and extended 5 cm below the right costal margin on inspiration. The spleen was not palpable. Neurological examination was within normal limits. Laboratory test results are shown in Table 1.

The child remained in the hospital for four days. Epistaxis ceased and she seemed more active and generally improved. Thereafter, at home, she appeared to be well, though with continued jaundice, until the onset of lethargy, vomiting, increasing jaundice, recurrent epistaxis and abdominal swelling during the first week of May. She was again admitted to hospital 9 May 1970 with jaundice and lethargy. A firm liver edge was palpable 8 cm below the right costal margin on inspiration and the splenic tip was palpable. There was mild pitting ankle edema and questionable shifting dullness in the abdomen. The patient remained in the hospital for ten days with gradual clinical improvement and some decrease in icterus. Shifting abdominal dullness disappeared and it was uncertain whether or not she did have ascites. A needle biopsy specimen of the liver was taken on the sixth hospital day, after improvement in the prothrombin time. In addition to the test results shown in Table 1, the hepatitis-associated antigen (HAA) test was positive, serum cerulo-

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No reprints available.

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TABLE 1.—*Laboratory Tests on Propositus Patient*

Date	*4/18/70*	*4/23/70*	*5/9/70*	*5/19/70*	*7/1/70*	*9/23/70*	*11/25/70*
Hb (gm per 100 ml)	9.7		10.1		12.0		
WBC (mm^3)	3200		8400		8800		
Bilirubin, total/direct (mg per 100 ml)	6.4/2.2	8.0/4.0	13.2/5.5	3.3/1.7	0.8/0.2	0.7/0.1	0.7/0.2
SGOT (Karmen units/ml)	> 4000		3960	184	136	150	215
SGPT (Karmen units/ml)	2840	750	1040	82	101		340
Alkaline phosphatase (B-L units per ml)	10		8	6	12		
Albumin/globulin (gm per 100 ml)		2.7/2.2	3.1/2.8	3.8/3.3	4.3/4.1	4.5/4.2	4.9/4.5
Prothrombin (percent)	< 5	59	32	100	100		
HAA	+		+		+		+

plasmin was normal, the Coombs test and the lupus erythematosus (LE) cell test were negative.

When the positive HAA test was obtained, a more detailed epidemiologic history was taken. The father had had hepatitis in 1967 and had been in hospital for one week. He admitted to occasional use of heroin intravenously and sometimes shared needles with friends. The mother had been admitted to a local hospital in 1968 with right upper quadrant pain and mild jaundice two weeks after delivery of her second child. At operation the gallbladder was gangrenous and cholecystectomy was performed. She received four blood transfusions during her stay in hospital. When tests were done on the father in July 1970, he was found to have a positive test for HAA, serum glutamic oxalic transaminase (SGOT) of 77 and glutamic pyruvic transaminase (SGPT) of 89 Karmen units per ml. The mother's serum was negative for HAA. A two-year-old sister of the patient had apparently been well with no episodes of jaundice but she had a positive test for HAA. SGOT was 77 and SGPT 103 units per ml, bilirubin was 0.8 mg per 100 ml and albumin was 4.4 and globulin was 3.2 gm per 100 ml. The paternal grandmother, who lives with the family, had been admitted to hospital in October 1970 with anorexia, fatigue and jaundice. Clinical and laboratory findings were typical for viral hepatitis. There was no history of injections or transfusions. The test for HAA was positive. She recovered satisfactorily in four weeks but the test for HAA remained positive in November 1970 and the SGOT remained elevated at 200 units per ml. In November 1970, the propositus, the younger sister and the father continued to have a positive test for HAA.

The patient remains clinically well but the liver and spleen are still palpable and transaminase levels are still elevated.

Discussion

DR. REYNOLDS:† It is now more than seven months since acute hepatitis developed in our patient and there are continued signs of activity of the disease judging from the increased serum transaminase activity and the positive HAA test. Probably, therefore, she has chronic hepatitis rather than a slowly resolving acute disease.

"Chronic hepatitis" is a relatively recently recognized syndrome with a wide clinical spectrum and probably multiple causes. Terminology, understandably, is in a state of flux. To most of us, chronic hepatitis indicates a combination of chronic liver disease and active hepatic inflammation. In the last analysis, "activity" is usually synonymous with an elevated serum transaminase level. This is probably a more reliable indication of active hepatic inflammation than such clinical features as jaundice, fatigue, right upper quadrant pain and hepatic tenderness, though these are often present concomitantly. Since there is *some* increase in serum transaminase in nearly all types of chronic liver disease, it is important to decide what level will be used to denote "active" hepatic inflammation. Soloway and colleagues at the Mayo Clinic have used a tenfold increase as a requirement for inclusion in a therapeutic trial of chronic active hepatitis.[1] Others use lower values, such as 200 Karmen units per ml, or have no fixed criteria. Chronicity in chronic hepatitis is indicated by a history of more than six months' duration or is implied by findings such as unusual firmness of the liver, splenomegaly, ascites, numerous spider angiomas or lowered serum albumin with raised globulin.

Our current classification of chronic hepatitis (subject to change without notice) is as follows (also see Table 2):

†Telfer Reynolds, M.D., Professor of Medicine.

TABLE 2.—*Classification of Chronic Hepatitis Currently Used by the Liver Service at Los Angeles County University of Southern California Medical Center*

Designation	*Etiology*	*Clinical Characteristics*	*Pathology*	*Serology*
I. Unresolved hepatitis (chronic persistent hepatitis, transaminitis)	Virus (SH and ? IH)	Persisting and fluctuating transaminase abnormality following viral hepatitis, without jaundice or clinical or laboratory evidence of progression to cirrhosis.	No cirrhosis nor fibrosis Uniform cobblestone arrangement of liver cells Occasional focal hepatocytolysis	HAA positive in 25% SMA negative LE negative
II. Chronic active viral hepatitis	Virus (SH)	Progression from icteric or anicteric long-incubation period, HAA-positive hepatitis to liver cirrhosis. Continuous mild or phasic activity with transaminase increase and occasionally jaundice.	Fibrosis and regeneration, usually cirrhosis Focal necrosis, cellular exudate, Kupffer's cell hyperplasia	HAA positive SMA negative LE negative
III. Chronic active lupoid hepatitis (plasma-cell hepatitis)	Uncertain (? immunologic)	Insidious onset Phasic episodes of jaundice and/or high transaminase activity superimposed on a gradually progressive coarsely nodular cirrhosis. Most patients are women and one-third have extrahepatic lupoid manifestations.	"	HAA negative SMA usually positive LE positive
IV. Chronic active toxic hepatitis	Oxyphenisatin (? other toxins)	Chronic jaundice and high transaminase activity progressing to liver cirrhosis.	"	HAA negative SMA often positive LE occasionally positive
V. Chronic active (cryptogenic) hepatitis (active chronic hepatitis, chronic aggressive hepatitis)	Uncertain	Similar to category III except for the absence of extrahepatic "lupoid" manifestations.	"	HAA negative SMA often positive LE negative

I. *Unresolved Viral Hepatitis*

During the past eight years, Dr. Redeker and Dr. Peters have collected a group of patients from the hepatitis follow-up clinic who appear to have recovered clinically but continue to have irregular elevation of serum transaminase activity.[2] Both SGOT and SGPT activities are increased to an approximately equal degree. Both may be perfectly normal for weeks at a time but more often than not they are abnormal, with values from two to as much as twenty times the upper limit of normal. The elevations are not accompanied by jaundice and usually bear no relationship to the generally benign clinical status of the patient. The liver is often palpable but does not become firm or greatly enlarged. The spleen is occasionally palpable but the clinical and laboratory features of liver cirrhosis have not yet developed in any of the patients, even after several years of observation. Other terms used for chronic hepatitis of this type are "transaminitis" and "chronic persistent hepatitis."[3] The ultimate fate of such patients is still uncertain.

II. *Chronic Active Viral Hepatitis*

Following an episode of icteric or anicteric viral hepatitis, such patients either have continuous low grade activity of their liver disease or phasic episodes of activity with jaundice and moderate or marked transaminase rise. The SGOT is usually higher than the SGPT. The clinical features of hepatic cirrhosis appear rather rapidly. The test for hepatitis-associated antigen is intermittently or continuously positive. Of approximately 25 patients that we have seen with this type of hepatitis, one-third have been followed from an episode of acute hepatitis and the remainder presumably have had a sub-clinical onset.

We have seen two children with chronic progressive liver disease whose illness seems to have begun with a typical episode of acute viral hepatitis but who have had a persistently negative test for HAA. This may mean that short-incubation-period hepatitis can cause chronic liver disease but we are uncertain of this and will probably remain so until some marker is available for "infectious" hepatitis. In our experience, most HAA-negative chronic hepatitis patients whose illness was said to begin with acute hepatitis have turned out to have clear evidence of chronic disease (that is, reversed albumin:globulin ratio) when the records of the acute illness were available for inspection.

III. *Chronic Active Lupoid Hepatitis*

Patients in this category usually have chronic liver disease when first seen, implying that the initial illness was anicteric and possibly asymptomatic. In the very few patients in whom we have witnessed what may have been the initial illness, there were invariably features that were unusual for acute viral hepatitis (a protracted course, a positive LE cell test, rapid development of hyperglobulinemia or unusual numbers of plasma cells on liver biopsy). In lupoid hepatitis, there is usually phasic rather than continuous activity superimposed on a gradually evolving coarsely-nodular cirrhosis. Most patients are female and the age range is wide, from childhood to the sixth or seventh decade. By definition, the LE cell phenomenon is demonstrable at some stage of the illness. Non-hepatic manifestations such as arthritis, autoimmune hemolytic anemia, skin rash, fever, nephritis or ulcerative colitis are present in approximately one-third of this group, but the liver disease is always the dominant feature.

IV. *Chronic Active Toxic Hepatitis*

We have been surprised to find recently that typical chronic active hepatitis can be caused by chronic or intermittent exposure to a laxative, oxyphenisatin. Long continued ingestion of this drug can cause either an acute viral hepatitis-like illness[4] or a more chronic liver disease with histologic and clinical features fitting the definition of chronic active hepatitis.[5] We know of two patients with chronic hepatitis and a positive LE cell test whose illness was probably caused by oxyphenisatin. This raises the disturbing possibility that other environmental toxins or drugs may cause chronic hepatitis.

V. *Chronic Active Hepatitis*

If the test for HAA is negative, the LE cell phenomenon is not demonstrable, and there is no recognizable toxin operative, we place patients with chronic hepatitis in this "unspecified" category. From a clinical standpoint, these patients resemble those with lupoid hepatitis except that there are fewer extrahepatic manifestations. The female preponderance and the wide age range are similar and the onset is usually insidious.

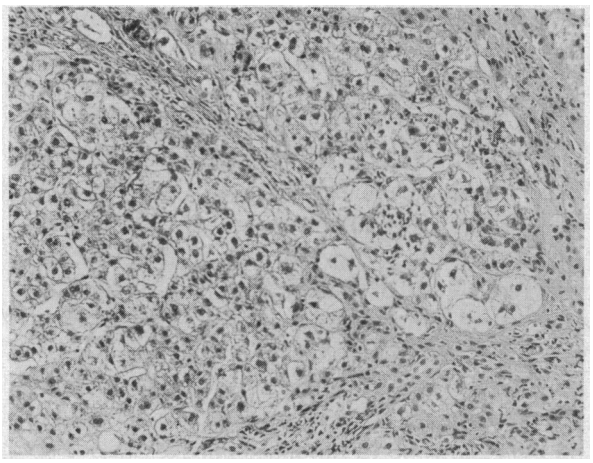

Figure 1.—Photograph of the microscopic appearance of liver showing swollen liver parenchymal cells and strands of fibrous tissue extending diagonally across the photograph. There are a few small foci where liver cells are undergoing destruction right above the diagonal band of fibrosis (H&E X 140).

Our patient today clearly belongs in the second category of chronic hepatitis and raises some interesting epidemiologic questions.

Dr. Peters will describe the liver biopsy and tell us something about the pathology and serologic tests in the various types of chronic hepatitis.

DR. PETERS:* The liver biopsy taken on May 19, 1970 (Figure 1) showed that the lobular architecture was completely distorted by regenerative nodules and thin fibrous septa. The liver cells were hydropic and numerous acinar structures and cobblestone-appearing arrangement of liver cells effaced the usual liver cord pattern. Within the poorly defined nodules were scattered foci of hepatocytolysis with lymphocytes and Kupffer cells filling the void left by the destroyed parenchymal cells. Kupffer cells, in general, were only slightly hyperplastic. There were occasional small canalicular bile plugs.

At one time we would have called this histologic lesion, chronic active hepatitis and would have considered it to be an autoimmune-related liver disorder.[6] The demonstration of HAA in the serum of this patient and other patients with similar hepatic morphologic changes has caused us to reevaluate chronic liver disease and its relationship to viral hepatitis.

To review a great deal of work very briefly, most of you are familiar with the story of Dr. Blumberg's identification of the hepatitis-associated antigen in 1965. At that time, Blumberg was screening sera of different racial groups in a search for genetic differences in serum proteins. Using agar gel as a diffusion media and plasma from hypertransfused hemophiliacs as antisera, he encountered a reaction against the serum of an Australian aborigine.[7] Dr. Blumberg named this antigen the Australia antigen. Many investigators still use this term, although in 1969 a National Institutes of Health conference at Yale University agreed on the use of the term *hepatitis-associated antigen* (HAA). Subsequent to Dr. Blumberg's discovery, several investigators, including Dr. Blumberg, demonstrated the appearance of HAA in the sera early in the course of long-incubation-type of viral hepatitis, whether transmitted parenterally or nonparenterally, but not in short-incubation hepatitis (epidemic or infectious hepatitis).[8-10] Krugman and his associates, who had worked for many years at the Willowbrook State School with a short-incubation, hepatitis-producing agent that they call MS-1, and a long-incubation hepatitis-producing agent that they called MS-2,[11] found that patients in whom hepatitis developed after inoculation with the MS-2 agent always began to have serum HAA just before the rise of SGPT activity. Those in whom hepatitis developed after inoculation with the MS-1 agent, never had HAA in their sera.[12] This supported Krugman's long-held contention that MS-2 was similar to or identical with the serum hepatitis agent, whereas MS-1 was probably the agent for infectious hepatitis.

Electron microscopic studies of the serum from patients who have demonstrable HAA show both round and filamentous 20 millimicron diameter particles in large abundance which can be shown to clump with HAA antisera[13,14] and, in addition, sparse 45 millimicron particles[15] (Figure 2). Biochemical analysis of the purified antigenic substance has demonstrated such a low nucleic acid content[16] that it is generally believed that the bulk of the antigenic material is not infective virus. However, a transfusion or inoculation of material that contains HAA causes some manifestations of viral hepatitis in about 75 percent of recipients.[17] Thus the evidence is quite good that a demonstrable and immunologically characteristic substance has finally been found that is related to the agent of one type of viral hepatitis—apparently the long incubation type (so-called serum hepatitis or hepatitis B by the older terminology). Obviously this

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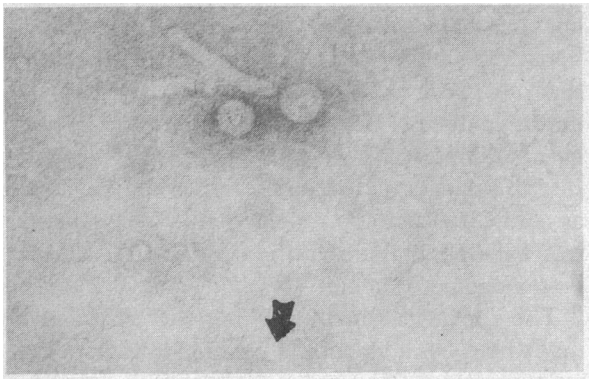

Figure 2.—Electron photomicrograph showing three types of particles commonly found in HAA positive sera. At the periphery (arrow) are the small 200 Å particles and in the center are the larger particles of 450 Å closely associated with a tubular segment (222,000 X).

marker constitutes a major advance in the study of viral hepatitis.

Now that a marker associated with acute long incubation viral hepatitis is fairly well established, we have the opportunity to study the fact and fiction of the maladies that have paraded under the term of chronic hepatitis.

Unresolved Hepatitis

In following the sera and histologic pattern in liver of patients convalescing from viral hepatitis, it is found that about one fourth of patients with unresolved hepatitis continue to have strong titers of HAA in sera. The most prominent, although usually overlooked, histologic feature in the livers of such patients is the cobblestone arrangement of parenchymal cells, a result of the continued regenerative activity. The liver cells are uniformly swollen and pale with slightly enlarged nuclei, and only sparse foci of hepatocytolysis can be found. The Kupffer cells are not prominent. To date, none of the patients followed has completely recovered; serial liver biopsy shows the histologic pattern retained for as long as we have followed the patients—eight years in some instances. Cirrhosis has not developed in any of the patients.

Persons with unresolved hepatitis probably are the endemic pool for serum hepatitis. If we assume that a similar proportion of patients whose initial viral disease was subclinical will also have unresolved viral hepatitis, the potential hepatitis pool becomes frightfully large.

Those who have a high risk of parenteral or nonparenteral contact with hepatitis and a low immunologic competence tend to acquire HAA with or without clinical disease and many continue to carry the antigen in their serum. Such patients include institutionalized children with Down's syndrome,[13] patients with lymphomatous disease who have received blood transfusions, patients on renal dialysis[18] and probably many other special groups. The incidence in the so-called normal population runs from less than 0.1 percent in parts of the United States to as high as 15.5 percent in Taiwan.[19-21] In the Los Angeles area, 0.3 percent of donors to the Red Cross have HAA positivity.[20]

Chronic Active Hepatitis Syndromes

The histologic picture of chronic active hepatitis is one that shows chronicity with a superimposed cytologic and inflammatory pattern of hepatitis. Usually by the time the biopsy is taken, the liver is truly cirrhotic. However, livers of some patients in the early stage may have only hepatic fibrosis in portal areas and some regenerative activity. Usually the areas of fibrosis are heavily infiltrated by lymphocytes and often by plasma cells. The liver parenchymal cells are no longer arranged in a cord pattern, they are ballooned and the liver cell nuclei are large with crisp nuclear membranes. The parenchyma is involved to a varying extent by focal hepatocytolysis with lymphocytes, plasma cells and Kupffer cells occupying the small foci vacated by the destroyed liver cells. Although "piecemeal" necrosis has been emphasized as a characteristic change occurring in the periphery of the nodules or periportal areas, we have not found this to be a distinctive feature of chronic active hepatitis, which instead is better characterized by the evidence of continuing regeneration and focal necrosis of liver cells. In contrast to ordinary viral hepatitis, there does not seem to be the centrolobular or centronodular accentuation of the parenchymal cell hydropic swelling, and cytologic changes are more uniform across the entire lobule or nodule but one nodule may differ from its neighbor. At times when the serum transaminase activity is diminished or nearly normal, there is less destructive activity histologically, and occasionally the regenerative and necrotizing processes will be entirely quiescent.

In light of recent demonstration of HAA in sera of many patients with chronic liver disease, some investigators have assumed that all instances of

chronic active hepatitis are due to viral hepatitis. However, in the patients we have observed, those with chronic active lupoid hepatitis do not have HAA. In a large enough series, one might expect to find an incidence of HAA positivity in the sera of patients with lupoid hepatitis similar to that in the rest of the population.

Chronic active viral hepatitis is histologically indistinguishable from chronic active lupoid hepatitis. We use the term chronic active *viral* hepatitis when patients have HAA in sera, and the term chronic active *lupoid* hepatitis when the LE phenomenon is demonstrable. The patient presented today belongs to the former group, HAA-positive viral hepatitis having developed in infancy, with progression to cirrhosis.

A large group of chronic hepatitis patients have negative HAA and no LE phenomenon but do have smooth muscle antibody (SMA) or antinuclear antibodies in sera, suggesting some immunologic component to their disease. Some of us believe the patients with chronic active hepatitis and SMA in sera really have the same basic disease as those who show, in addition, a positive LE cell preparation.

There still remains a group of patients who have neither HAA nor any immunologic serum reaction, and we call their disease simply chronic active hepatitis. These patients with negative HAA, SMA and LE cell tests may not be a uniform group and may have any of several different causes for their progressive liver disease and necrosis. Their disease may be a sequela of short-incubation viral hepatitis or prolonged exposure to a toxin, or it may be chronic active viral hepatitis or chronic active lupoid hepatitis with serum factors too weak to demonstrate.

A recent finding has been the high incidence of HAA in sera of patients who have liver cell carcinoma. We have demonstrated HAA in nine of thirteen non-alcoholic cirrhotic patients with liver cell carcinoma, but not in any of the patients with liver cell carcinoma arising on a background of alcoholic cirrhosis. Tong *et al* have found that 80 percent of 55 patients from Taiwan with liver cell carcinoma have HAA.[20] In Uganda, 40 percent of patients with liver cell carcinoma have HAA in the serum.[22] On the other hand, we have not found serologic tests characteristic of chronic active lupoid hepatitis in patients with liver cell carcinoma either from the United States or from Taiwan. We have not observed progression to liver cell carcinoma in any patients with chronic active lupoid hepatitis. In the past, we have tended to believe that neoplasia was simply an end stage of the natural course of development of cirrhosis. However, a difference in incidence of carcinoma occurring in patients with chronic active viral hepatitis as contrasted with chronic active lupoid hepatitis raises the possibility that the viral agent itself may be oncogenic.

The identification of the hepatitis antigen is made by several techniques. In the initial demonstration, Blumberg used a modification of Ouchterlony double diffusion in agar gel in which the precipitation arc develops between the antiserum and the serum containing the antigen. By use of a hexagonal pattern with a central well containing the antibody and the six peripheral wells containing four unknown and two antigen control sera, one can establish lines of identity in the precipitation arcs and also screen for antibody at the same time. The Ouchterlony technique remains the back-up method, but as originally described, it takes seven days to be certain that a specimen is negative, and only about 40 percent of patients with post-transfusion hepatitis have identifiable HAA even when SGPT activity is over 1000 Karmen units per ml.[21] The complement fixation technique was developed shortly after the importance of the antigen was recognized, and many laboratories feel that this is a highly sensitive method of detection. The development of automated complement fixation techniques that take only an hour offers some promise for mass screening if its sensitivity can be assured.

It was recognized by many investigators that the antigen moves during electrophoresis in the alpha-1 range and that the antibody, which is an IgG type, moves in the opposite direction. Therefore, during electrophoresis, antigen from the test serum moves toward the antibody in an opposing well. This technique, generally referred to as the immuno-electro-osmophoresis (IEOP), has stimulated a great deal of effort and many commercial kit type devices are now available on the market, some of them quite sensitive. The test can be performed at low or high voltage and takes between 35 minutes and two hours. Probably the most sensitive technique is the radio-immuno assay but the test time required and equipment necessary have kept this method in the research laboratory.

We found some time ago that a simple concentration of the test serum to tenfold its original

concentration by use of a polyacrilamide gel allowed us a better sensitivity with agar gel diffusion than the complement-fixation technique or the routine IEOP. We detected HAA in 83 percent of patients with post-transfusion hepatitis when SGPT activity was over 1000 units.[21] We still use this technique in our laboratory for establishing lines of identity of positive sera with control antigen. However, although 90 percent of the reactions are demonstrable in about 12 hours, some precipitation arcs still come up as late as six days. For screening of blood donors, this technique is obviously not satisfactory and we have found that the IEOP technique using tenfold concentrated sera gives us our best screening technique and highest sensitivity. We are hopeful that the recent development of a hemagglutination inhibition test with purified antigen attached to red cells will allow a simple, cheap, highly sensitive technique that will give rapid results.

DR. REDEKER:* There seems little doubt that today's patient now has cirrhosis. Finding the HAA present is of interest, but not a surprise. One is impressed with how quickly the features of cirrhosis followed the episode of apparent acute viral hepatitis. From both of these standpoints, this case is entirely like all of the few instances we have observed of clear-cut acute hepatitis progressing to cirrhosis. First, all of our patients following this course have been acutely and chronically HAA positive. Among adults, we have not recognized the development of cirrhosis from an initially HAA-negative type of hepatitis. Second, the progression to cirrhosis has been one of a rapid transition from acute-phase hepatitis to cirrhosis, usually in less than a year. It may well be that "infectious viral hepatitis" (short-incubation hepatitis or IH) does not progress to cirrhosis but that only HAA-positive hepatitis (long-incubation or serum hepatitis) has this potential. Such a conclusion will have to await the availability of other "markers" for the identification of infection with the IH virus or viruses.

The most common long term sequela of viral hepatitis is "unresolved viral hepatitis." This lesion is rarely associated with recurrent jaundice but instead is characterized by persistent or recurrent elevations of SGOT and SGPT, abnormal bromsulphalein retention, essentially normal values for serum proteins and generally good health. This would appear to be the disorder affecting the two-year-old sisters and the father of the patient. Each is HAA positive and presumably chronically so. Studies from our Hepatitis Unit show that in 9.7 percent of patients with acute HAA-positive hepatitis, "unresolved hepatitis" developed (Table 3). A significant fraction of these patients remain persistently HAA positive (approximately one-third). On the other hand, only 0.8 percent of the patients with complete biochemical resolution of their hepatitis show persistence of HAA. Over-all, 4.5 percent of initially HAA-positive patients remain so, no doubt becoming the endemic pool of carriers referred to by Dr. Peters.

TABLE 3.—*Follow-up Studies (6 to 18 Months) of 134 Patients with Acute Hepatitis and a Positive Test for* HAA

	Number	HAA *Positive*
Biochemically normal	121	1 (0.8%)
Unresolved hepatitis	13	5 (38%)
Total	134	6 (4.5%)

The question that must then be posed is whether these persistently HAA-positive patients are contagious. Certainly the presence of HAA seems to identify blood products that are infectious when administered parenterally. Gocke and colleagues[17] have shown a striking relationship between HAA in donor blood and the subsequent development of post-transfusion hepatitis. Krugman and Giles[23] demonstrated the infectivity of HAA-positive serum injected intramuscularly. Probably more important in relation to the present case, these investigations also demonstrated infectivity of HAA-positive serum when fed orally. The incubation period was long, characteristic of the viral agent rather than the route of administration. Supporting this was the earlier observation of Mirick and Shank[24] of secondary cases of hepatitis among contacts of patients with post-inoculation serum hepatitis (long-incubation type). With the advent of HAA testing, most investigators were startled to recognize that, at least among adults, approximately 50 percent of all apparently non-parenteral hepatitis was HAA-positive, presumably, due to infections with the SH virus. We have observed a number of instances of acute hepatitis occurring among household contacts of persistently HAA-positive patients with no evidence for any parenteral contact. Thus, it appears that (a) serum positive for HAA is infectious and (b) HAA-positive patients are potentially infectious by some form of person-

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to-person contact. It should be pointed out that direct challenge has only been done with serum per os, not feces. Fecal shedding of HAA has not yet been demonstrated, although, probably the stool could be periodically contaminated by HAA-positive blood.

Very likely the original patient with hepatitis in this family was the father, who has now become a hepatitis carrier. The younger sibling probably contracted hepatitis from the father and now is also a carrier. Either could have provided the source of infection for the propositus patient. The most recent instance of acute hepatitis in the grandmother further supports the concept that the carriers in this household are infectious.

The question of gamma globulin prophylaxis for HAA-positive hepatitis contacts must be raised. Unfortunately, there is no reason to believe that conventional gamma globulin provides any element of protection or modification for HAA-positive hepatitis. Krugman was unable to demonstrate any neutralization of the serum hepatitis agent when gamma globulin was mixed with SH-containing serum, then injected intramuscularly.[23] In a recent study of our own of hospital personnel who had been exposed to HAA-positive serum by an accidental needle stick, it was found that hepatitis developed in six of fifteen (40 percent) although each had received 20 ml of gamma globulin. Supporting these observations is the recent report of the National Cooperative Post-Transfusion Hepatitis Study showing no protection from hepatitis with 10 ml of gamma globulin given on three occasions after transfusion.[25] The virus associated with HAA may be of very low immunogenic potency, since it is rare to observe detectable antibody during recovery from hepatitis and since none has been detectable in standard gamma globulin preparations.

DR. REYNOLDS: With evidence of hepatitis in two young children, one could speculate about transplacental infection from the mother. Dr. Schweitzer, of our Hepatitis Unit, has collected some interesting data bearing on this possibility.

DR. SCHWEITZER:* The hepatitis-associated antigen was studied in 44 mother-infant pairs. These pairs were made up of women in whom typical acute viral hepatitis developed during pregnancy or within six months of delivery and whose newborn were tested for HAA at least one time. The purpose of the study was to determine the frequency of transmission of HAA or of viral hepatitis from mother to infant, to consider the possible mode of such transmission, and to study the course of this illness in newborn children. Our early results have been reported.[26]

Twenty mothers were HAA-positive during acute hepatitis, and seven of their babies were found to be HAA-positive. Seventeen women were HAA-negative while ill, and seven were not tested. None of their babies became HAA-positive.

There was a total of seven HAA-positive babies. One has been HAA-positive for more than 15 months without any sign of hepatitis. Another has been HAA-positive for more than 12 months with prolonged, subclinical hepatitis which has now apparently resolved. Two have remained HAA-positive for over five months without apparent hepatitis. One has been HAA-positive for over five months with prolonged sub-clinical hepatitis. Another was found to be HAA-positive at ten months of age and sub-clinical hepatitis has since developed. One has recently been found to be HAA-positive at seven weeks of age with no signs of hepatitis as yet.

All mothers of the HAA-positive babies were HAA-positive at the time of their acute hepatitis. In one the onset of the hepatitis was six weeks before delivery, in three the onset was at the time of delivery, and in three it was one month postpartum.

In ten cases cord blood was tested for HAA and all were found to be negative. In four cases the mothers were HAA-positive at delivery. The babies of two of these subsequently became HAA-positive and the babies of the other two remained HAA-negative. Six mothers were HAA-negative at delivery and none of their babies became HAA-positive.

The data demonstrate that the transmission of HAA from mother to infant is not uncommon (35 percent in our cases). The mode of transmission is less clear. Four of the cases suggest that HAA may not cross the placental barrier: The mothers' serum was HAA-positive at the time of delivery, the umbilical cord samples were HAA-negative, and two babies of these women subsequently became HAA-positive.

The hepatitis-associated antigen seems to remain in the serum of affected infants for long and perhaps indefinite periods. None of our HAA-positive infants have become HAA-negative and one has been followed for more than 15 months. When hepatitis develops in these infants it is sub-clinical

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and detectable only by biochemical tests (for example, SGPT in a 700 to 1600 range). The course is several months and the end results remain unknown. One is fearful that hepatic cirrhosis secondary to chronic viral hepatitis may develop in some of these children.

DR. REYNOLDS: From what we have heard, we can conclude that the father is the probable source of infection in the family of today's patient and that the prognosis for her is limited, while the sibling and father may remain asymptomatic carriers indefinitely. Perhaps of more than passing interest is the fact that the four HAA carriers in this family are blood relatives, giving support to the theory of Blumberg and colleagues that a genetic trait is involved.[19]

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